Figure 18

SEQ ID NO:1

Homo Sapiens Ephrin type-B receptor 4 Precursor (EphB4)

Added Q

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21	DTATALTPAW	MENPYIKVDT	VAAEHLTRKR	PGAEATGKVN	VKTLRLGPLS	KAGFYLAFQD
181	QGACMALLSL	HLFYKKCAQL	TVNLTRFPET	VPRELVVPVA	GSCVVDAVPA	PGPSPSLYCR
241	EDGQWAEQPV	TGCSCAPGFE	AAEGNTKCRA	CAQGTFKPLS	GEGSCQPCPA	NSHSNTIGSA
301	VCQCRVGYFR	ARTDPRGAPC	TTPPSAPRSV	VSRLNGSSLH	LEWSAPLESG	GREDLTYALR
361	CRECRPGGSC	APCGGDLTFD	PGPRDLVEPW	VVVRGLRPDF	TYTFEVTALN	GVSSLATGPV
421	PFEPVNVTTD	REVPPAVSDI	RVTRSSPSSL	SLAWAVPRAP	SGAVLDYEVK	YHEKGAEGPS
481	SVRFLKTSEN	RAELRGLKRG	ASYLVQVRAR	SEAGYGPFGQ	EHHSQTQLDE	SEGWREQLAL
541	IAGTAVVGVV	LVLVVIVVAV	LCLRKQSNGR	EAEYSDKHGQ	YLIGHGTKVY	IDPFTYEDPN
601	EAVREFAKEI	DVSYVKIEEV	IGAGEFGEVC	RGRLKAPGKK	ESCVAIKTLK	GGYTERQRRE
661	FLSEASIMGQ	FEHPNIIRLE	GVVTNSMPVM	ILTEFMENGA	LDSFLRLNDG	QFTVIQLVGM
721	LRGIASGMRY	LAEMSYVHRD	LAARNILVNS	NLVCKVSDFG	LSRFLEENSS	DPTYTSSLGG
781	KIPIRWTAPE	AIAFRKFTSA	SDAWSYGIVM	WEVMSFGERP	YWDMSNQDVI	NAIEQDYRLP
841	PPPDCPTSLH	QLMLDCWQKD	RNARPRFPQV	VSALDKMIRN	PASLKIVARE	NGGASHPLLD
901	QRQPHYSAFG	SVGEWLRAIK	MGRYEESFAA	AGFGSFELVS	QISAEDLLRI	GVTLAGHQKK
961	ILASVQHMKS	QAKPGTPGGT	GGPAPQY			

Added Y

Added N

Exhibit A

VERSION 2

☐ **1:** NP_004435. Reports ...[gi:17975770] The record has been replaced by NP_004435.3

Comment Features Sequence

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LOCUS       NP_004435                 987 aa            linear   PRI 05-APR-2003
DEFINITION  ephrin receptor EphB4 precursor; Ephrin receptor EphB4 (hepatoma
            transmembrane kinase); Tyro11; ephrin receptor EphB4; hepatoma
            transmembrane kinase [Homo sapiens].
ACCESSION   NP_004435
VERSION     NP_004435.2  GI:17975770
DBSOURCE    REFSEQ: accession NM_004444.2
KEYWORDS    .
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (residues 1 to 987)
  AUTHORS   Steinle,J.J., Meininger,C.J., Forough,R., Wu,G., Wu,M.H. and
            Granger,H.J.
  TITLE     Eph B4 receptor signaling mediates endothelial cell migration and
            proliferation via the phosphatidylinositol 3-kinase pathway
  JOURNAL   J. Biol. Chem. 277 (46), 43830-43835 (2002)
   PUBMED   12235151
  REMARK    GeneRIF: Eph B4 stimulates migration and proliferation and may play
            a role in angiogenesis
REFERENCE   2  (residues 1 to 987)
  AUTHORS   Suenobu,S., Takakura,N., Inada,T., Yamada,Y., Yuasa,H., Zhang,X.Q.,
            Sakano,S., Oike,Y. and Suda,T.
  TITLE     A role of EphB4 receptor and its ligand, ephrin-B2, in
            erythropoiesis
  JOURNAL   Biochem. Biophys. Res. Commun. 293 (3), 1124-1131 (2002)
   PUBMED   12051776
  REMARK    GeneRIF: role of EphB4 receptor in erythropoiesis
REFERENCE   3  (residues 1 to 987)
  AUTHORS   Wang,Z., Miura,N., Bonelli,A., Mole,P., Carlesso,N., Olson,D.P. and
            Scadden,D.T.
  TITLE     Receptor tyrosine kinase, EphB4 (HTK), accelerates differentiation
            of select human hematopoietic cells
  JOURNAL   Blood 99 (8), 2740-2747 (2002)
   PUBMED   11929761
  REMARK    GeneRIF: accelerates differentiation of select human hematopoietic
            cells
REFERENCE   4  (residues 1 to 987)
  AUTHORS   Wilson,M.D., Riemer,C., Martindale,D.W., Schnupf,P., Boright,A.P.,
            Cheung,T.L., Hardy,D.M., Schwartz,S., Scherer,S.W., Tsui,L.C.,
            Miller,W. and Koop,B.F.
  TITLE     Comparative analysis of the gene-dense ACHE/TFR2 region on human
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chromosome 7q22 with the orthologous region on mouse chromosome 5
JOURNAL Nucleic Acids Res. 29 (6), 1352-1365 (2001)
PUBMED 11239002
REFERENCE 5 (residues 1 to 987)
AUTHORS Berclaz,G., Andres,A.C., Albrecht,D., Dreher,E., Ziemiecki,A., Gusterson,B.A. and Crompton,M.R.
TITLE Expression of the receptor protein tyrosine kinase myk-1/htk in normal and malignant mammary epithelium
JOURNAL Biochem. Biophys. Res. Commun. 226 (3), 869-875 (1996)
PUBMED 8831703
REFERENCE 6 (residues 1 to 987)
AUTHORS Bennett,B.D., Wang,Z., Kuang,W.J., Wang,A., Groopman,J.E., Goeddel,D.V. and Scadden,D.T.
TITLE Cloning and characterization of HTK, a novel transmembrane tyrosine kinase of the EPH subfamily
JOURNAL J. Biol. Chem. 269 (19), 14211-14218 (1994)
PUBMED 8188704
REFERENCE 7 (residues 1 to 987)
AUTHORS Andres,A.C., Reid,H.H., Zurcher,G., Blaschke,R.J., Albrecht,D. and Ziemiecki,A.
TITLE Expression of two novel eph-related receptor protein tyrosine kinases in mammary gland development and carcinogenesis
JOURNAL Oncogene 9 (5), 1461-1467 (1994)
PUBMED 8152808
COMMENT REVIEWED REFSEQ: This record has been curated by NCBI staff. The reference sequence was derived from U07695.1.
[WARNING] On Jul 11, 2003 this sequence was replaced by gi:32528301.
→ On Dec 21, 2001 this sequence version replaced gi:4758290.

Summary: Ephrin receptors and their ligands, the ephrins, mediate numerous developmental processes, particularly in the nervous system. Based on their structures and sequence relationships, ephrins are divided into the ephrin-A (EFNA) class, which are anchored to the membrane by a glycosylphosphatidylinositol linkage, and the ephrin-B (EFNB) class, which are transmembrane proteins. The Eph family of receptors are divided into 2 groups based on the similarity of their extracellular domain sequences and their affinities for binding ephrin-A and ephrin-B ligands. Ephrin receptors make up the largest subgroup of the receptor tyrosine kinase (RTK) family. The protein encoded by this gene binds to ephrin-B2 and plays an essential role in vascular development.

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	/EC_number="2.7.1.112"
	/note="Ephrin receptor EphB4 (hepatoma transmembrane kinase); Tyro11; ephrin receptor EphB4"
sig_peptide	1..15
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                     /db_xref="CDD:pfam00041"
     Region          615..874
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                     /note="TyrKc; Tyrosine kinase, catalytic domain"
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                     mediates homodimerisation"
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      241 edgqwaeqpv tgcscapgfe aaegntkcra caqgtfkpls gegscqpcpa nshsntigsa
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Exhibit B

☐ 1: NP_004435. Reports ephrin receptor E...[gi:32528301]

Comment Features Sequence

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LOCUS       NP_004435                 987 aa            linear   PRI 29-APR-2008
DEFINITION  ephrin receptor EphB4 precursor [Homo sapiens].
ACCESSION   NP_004435
VERSION     NP_004435.3  GI:32528301
DBSOURCE    REFSEQ: accession NM_004444.4
KEYWORDS    .
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini;
            Catarrhini; Hominidae; Homo.
REFERENCE   1  (residues 1 to 987)
  AUTHORS   Alam,S.M., Fujimoto,J., Jahan,I., Sato,E. and Tamaya,T.
  TITLE     Coexpression of EphB4 and ephrinB2 in tumour advancement of ovarian
            cancers
  JOURNAL   Br. J. Cancer 98 (4), 845-851 (2008)
   PUBMED   18231102
  REMARK    GeneRIF: Overexpression of EphB4 is associated with tumour
            advancement of ovarian cancers
REFERENCE   2  (residues 1 to 987)
  AUTHORS   Tachibana,M., Tonomoto,Y., Hyakudomi,R., Hyakudomi,M., Hattori,S.,
            Ueda,S., Kinugasa,S. and Yoshimura,H.
  TITLE     Expression and prognostic significance of EFNB2 and EphB4 genes in
            patients with oesophageal squamous cell carcinoma
  JOURNAL   Dig Liver Dis 39 (8), 725-732 (2007)
   PUBMED   17611172
  REMARK    GeneRIF: EphB4 expression was found in 44 (72.1%) out of 61 cancer
            tissues analysed.
REFERENCE   3  (residues 1 to 987)
  AUTHORS   Foubert,P., Silvestre,J.S., Souttou,B., Barateau,V., Martin,C.,
            Ebrahimian,T.G., Lere-Dean,C., Contreres,J.O., Sulpice,E.,
            Levy,B.I., Plouet,J., Tobelem,G. and Le Ricousse-Roussanne,S.
  TITLE     PSGL-1-mediated activation of EphB4 increases the proangiogenic
            potential of endothelial progenitor cells
  JOURNAL   J. Clin. Invest. 117 (6), 1527-1537 (2007)
   PUBMED   17510705
  REMARK    GeneRIF: activation of EphB4 enhances proangiogenic capacity
            through induction of PSGL-1 expression and adhesion to E selectin
            and P selectin
REFERENCE   4  (residues 1 to 987)
  AUTHORS   Kumar,S.R., Masood,R., Spannuth,W.A., Singh,J., Scehnet,J.,
            Kleiber,G., Jennings,N., Deavers,M., Krasnoperov,V., Dubeau,L.,
            Weaver,F.A., Sood,A.K. and Gill,P.S.
  TITLE     The receptor tyrosine kinase EphB4 is overexpressed in ovarian
```

cancer, provides survival signals and predicts poor outcome
JOURNAL Br. J. Cancer 96 (7), 1083-1091 (2007)
PUBMED 17353927
REMARK GeneRIF: Overexpression of EphB4 is associated with ovarian cancer
REFERENCE 5 (residues 1 to 987)
AUTHORS Limbourg,A., Ploom,M., Elligsen,D., Sorensen,I., Ziegelhoeffer,T., Gossler,A., Drexler,H. and Limbourg,F.P.
TITLE Notch ligand Delta-like 1 is essential for postnatal arteriogenesis
JOURNAL Circ. Res. 100 (3), 363-371 (2007)
PUBMED 17234965
REMARK GeneRIF: Notch signaling by induction of Dll1 was necessary & sufficient to induce EphB4-dependent branching morphogenesis in human arterial EC.
REFERENCE 6 (residues 1 to 987)
AUTHORS Zhou,R.
TITLE The Eph family receptors and ligands
JOURNAL Pharmacol. Ther. 77 (3), 151-181 (1998)
PUBMED 9576626
REMARK Review article
REFERENCE 7 (residues 1 to 987)
AUTHORS Flanagan,J.G. and Vanderhaeghen,P.
TITLE The ephrins and Eph receptors in neural development
JOURNAL Annu. Rev. Neurosci. 21, 309-345 (1998)
PUBMED 9530499
REMARK Review article
REFERENCE 8 (residues 1 to 987)
AUTHORS Berclaz,G., Andres,A.C., Albrecht,D., Dreher,E., Ziemiecki,A., Gusterson,B.A. and Crompton,M.R.
TITLE Expression of the receptor protein tyrosine kinase myk-1/htk in normal and malignant mammary epithelium
JOURNAL Biochem. Biophys. Res. Commun. 226 (3), 869-875 (1996)
PUBMED 8831703
REFERENCE 9 (residues 1 to 987)
AUTHORS Bennett,B.D., Wang,Z., Kuang,W.J., Wang,A., Groopman,J.E., Goeddel,D.V. and Scadden,D.T.
TITLE Cloning and characterization of HTK, a novel transmembrane tyrosine kinase of the EPH subfamily
JOURNAL J. Biol. Chem. 269 (19), 14211-14218 (1994)
PUBMED 8188704
REFERENCE 10 (residues 1 to 987)
AUTHORS Andres,A.C., Reid,H.H., Zurcher,G., Blaschke,R.J., Albrecht,D. and Ziemiecki,A.
TITLE Expression of two novel eph-related receptor protein tyrosine kinases in mammary gland development and carcinogenesis
JOURNAL Oncogene 9 (5), 1461-1467 (1994)
PUBMED 8152808
REMARK Erratum:[Oncogene 1994 Aug;9(8):2431]
COMMENT REVIEWED REFSEQ: This record has been curated by NCBI staff. The reference sequence was derived from CB962032.1, BC052804.1 and AY056048.1.
→ On Jul 11, 2003 this sequence version replaced gi:17975770.

Summary: Ephrin receptors and their ligands, the ephrins, mediate numerous developmental processes, particularly in the nervous system. Based on their structures and sequence relationships, ephrins are divided into the ephrin-A (EFNA) class, which are anchored to the membrane by a glycosylphosphatidylinositol linkage, and the ephrin-B (EFNB) class, which are transmembrane proteins. The Eph family of receptors are divided into 2 groups based on the similarity of their extracellular domain sequences and their

affinities for binding ephrin-A and ephrin-B ligands. Ephrin receptors make up the largest subgroup of the receptor tyrosine kinase (RTK) family. The protein encoded by this gene binds to ephrin-B2 and plays an essential role in vascular development.

Publication Note: This RefSeq record includes a subset of the publications that are available for this gene. Please see the Entrez Gene record to access additional publications.

FEATURES Location/Qualifiers

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Last update: Tue, 29 Apr 2008 Rev. 126150